Cellular-based Computational Model of hMSC Differentiation into Neuronal Lineage on Nanofibrous PCL- Graphene Scaffolds

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Abstract

In the last decade, stem cell research and nanotechnology have played a crucial role in the rapid advancement of tissue engineering. In this project ,we utilize biological observations and develop a computational model, using Cellular Potts Model (a.k.a the Glazier-Graner-Hogeweg model), a lattice-based, cellular level computational framework that accurately describes biological phenomena including stem cell differentiation. Particularly we focus on cellular level interactions of hMSC derived neuronal cells on a Poly(ε-caprolactone) (PCL)-graphene scaffolds which are proven to provide better protein and cell adhesion. In this study, the Cellular Potts Model is used to design a dynamic microenvironment for cellular organization and its functioning at a Nano-scale level and also study the cells-biomaterial interactions.

Introduction

Regeneration of the neuronal cells due to injury or degenerative diseases, is very limited. In this study ,we use a Poly(ε-caprolactone) (PCL)-graphene scaffolds to grow hMSC derived neuronal cells. This scaffolds have shown better cell guidance and improved electrical interactions of neuronal cells. The purpose of this study is to investigate cellular level interactions of cells with the scaffold using the Cellular Potts Model(CPM).CPM is a lattice-based, cellular level computational framework that accurately describes biological phenomena and is based on a statistical model. The interactions such as cell-cell, cell-extracellular matrix adhesion and cellular motility contribute to the system's energy given by a function known as Hamiltonian which manages the lattice rearrangement using the stochastic Monte Carlo's model by minimizing the total energy. The Hamiltonian function is given as :

$$H(t) = Hadhesion(t) + Hconstraint(t) + Hforce(t)$$

$$Hadhesion(t) = \sum_{x,x' \epsilon \Omega'_x} J_{\tau(\sum(x),\tau(\sum s'(x')} \ (t)$$

$$Hconstraint(t) = \sum_{\sum}^{\sigma} \sum_{i-constraint} \ \lambda_{\sum}^{\sigma i}(t) \ [a_{\sum\sigma}^{i} \ (t) - A_{\sum\sigma}^{i} \ (t)]^2$$

$$Hforce(t) = \sum_{x \in \sum}^{\sigma} \sum_{k-force} \mu_{\sum(x)}^{k} \ (t) F^{k} \ (t) \cdot r_x$$

Methodology

CompuCell3d is the environment we use to implement and simulate the CPM model. In our simulation we set 1 pixel to correspond to 4μm and the time, which is given by **Monte Carlo Steps (MCS)**, to corresponds to 2s of the real experimental time. The Cell Type plugin and Contact plugin are specified with our cells being neuron ,PCL ,graphene and the respective contact energies between cells and scaffolds.
The **External Potential Plugin** is used to assign force to the cells in order to move in a particular direction. In order to make the cells grow and divide , Mitosis ,was implemented as a Steppable function.

Parameter	Description
$A_C^{Surface}$	Surface of neuron cells
$A_C^{Perimeter}$	Perimeter of neuron cells
$\lambda_C^{Surface}$	Compressibility of neuron cells
$\lambda_C^{Perimeter}$	Stiffness of neuron cells
$J_{C,C}$	Cell-cell adhesion
$J_{C,M}$	Cell-matrix adhesion
T	Motility of the neuron cells

Table1. Main parameters and their description

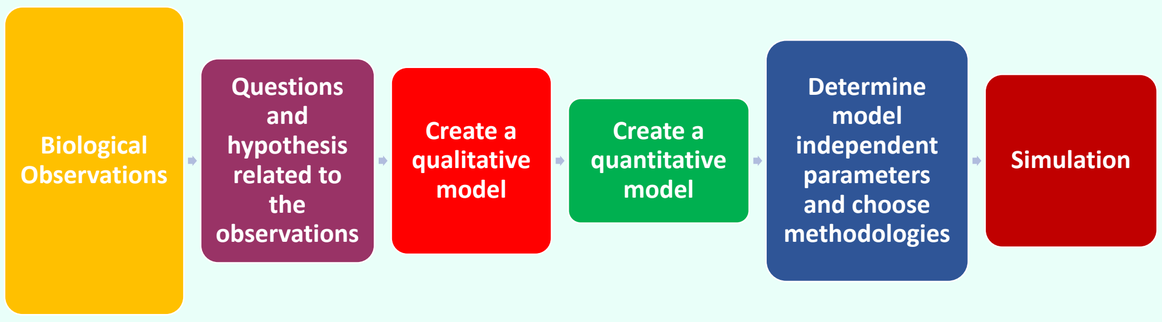
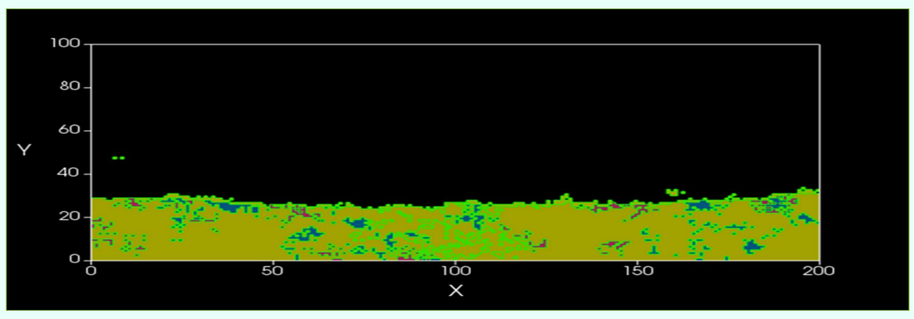


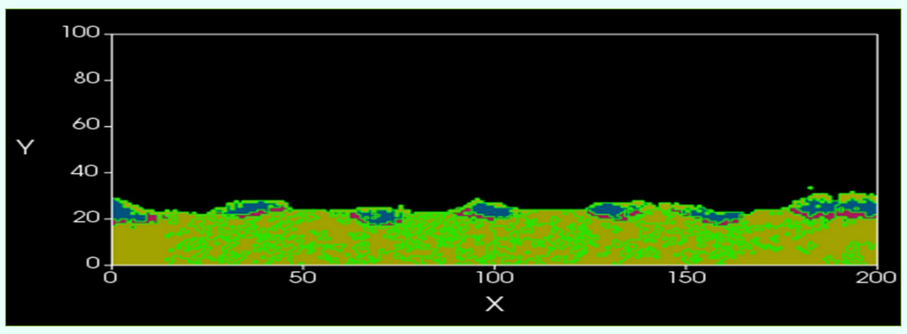
Fig.1.Biological Modelling Workflow

Results

After letting the simulation run for 150000 MCS , we found out that neuron cells tend to move towards the areas where graphene is more concentrated
This results are satisfying when compared with the experimental observations, which show a cell alignment when a particular concentration of graphene is used. However ,further simulation including the alteration of cell shape and the alignment of cells due to the tendency to go up gradient when the rigidity of the substrate is increased , need to be done.



A



B

Fig.2 A. Compucell3d simulation; the brown cells are the PCL fibers , the blue are the neuron cells and the purple represent graphene. X-Y axis represent the lattice dimensions. The screenshot is taken at MCS=10 . **B**. After certain MCS we observe that the neuron cells are concentrated near the graphene .

Conclusion

CPM model is used in various applications and its predictive power can save a lot of experimental time and cost . In our study CPM is promising to analyse the behaviour of the neuronal cells , their motility and the alignment in the scaffold. In CompuCell3d simulation ,further mechano-transduction studies have to be done in order to quantify the cell alignment in the scaffold and also different representation of the fibrous scaffold as random mashed lines need to be implemented in our future simulations.

References

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